COMPUTER AIDED ANALYSIS OF BRAIN ELECTRICAL ACTIVITY[1, 2]

UNPUBLISHED PRELIMINARY DATA

N65-83265

Ordenne

Frank Morrell, M.D. and
Lenore Morrell, Ph.D.

Division of Neurology
Stanford University School of Medicine
Palo Alto, California

Nasa CR 57789

[redacted] — 12-31-64

Introduction

What follows is essentially a progress report on the past two years work in a laboratory deriving its main support from a NASA grant. Although all the studies to be described are interrelated, they fall into several readily definable subject areas which will be discussed separately. These include (1) relation of background EEG to vigilance behavior, (2) relation of evoked potentials to reaction-time behavior, (3) period analysis of pre-signal background EEG, (4) sensory interactions at a cortical, electrophysiological level, (5) observations on the spatial distribution of evoked potentials. Implications for models of neuronal function and for the detailed study of maturation and of certain clinical conditions.

Accordingly, the first portion of this report outlines some observations concerning the relationship between EEG potentials recorded from persons performing simple detection-response tasks and the level of performance in those tasks.

[1]Report presented at the Executive Scientific Session of the NASA Conference "Analysis of Central Nervous System and Cardiovascular Data using Computer Methods," October 28, 29 and 30, 1964, in Washington, D.C.

[2]This work has been supported by NASA grant NsG 215-62, and USPHS grants FR-81 and FR-70.

I. Background EEG and Reaction Time

We had previously described (Morrell and Morrell, [illegible]) the fact that normal and sleep-deprived subjects in a prolonged vigilance task (such as counting the number of aperiodically presented flashes of light, or indicating detection of each light flash by pressing a response key) exhibit pronounced but systematic oscillations in the level of their performance as measured by the latency of a motor response to a critical signal. These oscillations in efficiency of vigilance behavior are related to phasic shifts in background EEG patterns.

Figure 1 illustrates the basic phenomenon. EEG tracings from the

---

INSERT FIG. 1 ABOUT HERE

---

derivations indicated are seen in the upper three channels. The signal marker on the fourth channel denotes the onset of a bright brief (50 msec.) flash of light delivered to the full visual field. The motor response of the subject signifying detection of the light flash is shown by another signal marker on the fifth channel. Latency of motor response in msec. (measured by an electronic clock) is written beside each response marker.

The midportion of the EEG tracing in Fig. 1 shows a burst of relatively high voltage, almost monorhythmic theta activity of several seconds duration. A light flash delivered coincident with the theta burst failed to elicit signal detection behavior (response failure). Yet immediately prior to the failure and immediately afterward the signal was detected and responded to rapidly. Even when the theta burst was of much briefer duration than that shown in the previous example,

so that centrally delivered signals may fail to be detected (Fig. 2).

INSERT FIG. 2 ABOUT HERE

On the other hand, signals which occur only a second or two after a theta burst when the background alpha activity has resumed result in prompt detection and rapid response times (Figs. 3 and 4).

INSERT FIG. 3 ABOUT HERE

Figure 4 is of particular interest in this regard since one of the shortest reaction times exhibited by the subject (340 msec.) occurred almost immediately following a theta burst.

INSERT FIG. 4 ABOUT HERE

However, alpha activity does not always resume promptly after an episode of theta rhythm. Sometimes the theta burst trails off into a poorly defined background state characterized by a mixture of fast and slow frequencies of very low amplitude. Further definition of this background state will be referred to later but it may be noted here that response failure may occur under such conditions as well (Fig. 5).

INSERT FIG. 5 ABOUT HERE

Much more rarely an effect entirely opposite to that discussed above can be noted. Instead of failing to detect a signal the subject may respond when no signal had been presented, i.e. an error of commission. [illegible] that such false responses are also associated with episodes of theta rhythm similar to those noted in the cases of response failures just discussed.

INSERT FIG. 6 ABOUT HERE

These sudden phasic shifts in EEG patterns occurred in all subjects tested, even the most highly practiced and highly motivated. They appeared more frequently with increased time on task for some subjects but were present invariably in experiments lasting as little as 2[illegible] minutes.

The EEG changes described thus far are clear and unambiguous. There is no doubt that patterns such as the "theta burst" could be recognized automatically by a suitably programmed computer. Detection of more subtle alterations in background rhythms will be dealt with below but first it is pertinent to indicate just how reliable is the correlation between the behavioral criterion of response failure and the presence of theta activity in the EEG in the interval prior to stimulus delivery.

The 12 normal subjects participating in this experiment provided 1,847 stimulus-response trials. [illegible]19 of these trials occurred when the background EEG contained slow frequencies ([illegible] cycles/second or slower). Response failure occurred in 1[illegible] of these trials or 2[illegible]%. Under the conditions of this experiment, therefore, a stimulus delivered at a time when the background EEG contained

frequencies of 7 cycles/second or slower was not detected in 1 out of every 3 trials. On the other hand, there was a total of 139 complete response failures in the entire experiment of which 110 or 79% occurred during slow wave epochs (Table I).

INSERT TABLE I ABOUT HERE

Although failure to respond occurred in only 7.5% of all stimulations, the delineation of an electroencephalographic pattern sufficiently unique to allow prediction of almost 80% of all instances of this class of behavior has obvious practical implications. For example, an astronaut in space flight may be required to execute certain maneuvers upon receipt of a command from ground stations. Failure to respond under such circumstances could be disastrous. An automatic on-line EEG monitor using nothing more sophisticated than a filter capable of detecting frequencies between 1 and 7 cps and a suitable electronic counter would provide a method of predicting at least 80% of the failures.

What about the remaining 20%? What about the electrophysiological correlates of more fine-grained assessment of behavior such as longer or shorter reaction-times? Is variability itself a parameter which should be separately examined and does increased or decreased variability correlate with particular electrophysiological measures? Answers to some of these questions have begun to emerge.

To begin with, a rough classification of the frequency composition of the 1-second epoch prior to stimulus delivery was made. Three groups were defined:

(1) alpha - continuous 8-13 cps throughout the epoch; (2) slow - activity in the range of 4-7 cps either throughout the epoch or at least three such waves immediately preceding the stimulus; (3) mixed - a mixture of low voltage fast and low voltage theta.

INSERT TABLE II ABOUT HERE

Table II shows the mean, median and range of reaction times for each of the preceding categories. The actual range of reaction-times is a better single measure of variability rather than the standard deviation since the population of responses was not "normally" distributed. However it is instructive to compare the mean with the median in each category. The degree to which the median approximates the true mean reflects the relative "normality" of the distribution within each sub-group. Thus in the "alpha" and "slow" categories the median is close to the mean. In the "mixed" category the two figures differ by [illegible] suggesting that this group contributes largely to the skewing of the entire population sample.

In any case it is clear that the median (or mean) reaction-time is shortest for the "alpha" category and longest for the "slow" while the "mixed" group falls in between. Furthermore the range is wider for the "slow" category than for the others despite the fact that response failures were necessarily eliminated from the tabulation. The differences noted are significant at the 0.01 level for the grouped data as well as for each individual subject.

Nevertheless, the range of response-times for each background frequency

categories show wide overlap, thus precluding any simple prediction of a particular response latency (excluding failures) as a function of these stimulus-background states, at least on the basis of criteria applied so far.

An examination was also conducted of the relationship between the direction of change of RT latency and the actual sequence of occurrence of background EEG categories. Successive pairs of trials were evaluated. Reaction times were scored as either increased, decreased, or unchanged from trial to trial. The three classes of EEG activity yielded nine possible sequence pairs, that is "alpha" followed by "alpha," "mixed," or "slow," "slow" followed by "alpha," "mixed," or "slow," etc. Given types of epoch tended to cluster in time (i.e., given an alpha background the next most likely background was alpha also). Quantitatively, 79% of all measured EEG background states recurred on the next succeeding trial; 64% of such measurements remained constant for at least three trials, 42% over at least four trials, and 29% showed constancy for five or more successive trials. Although these figures indicate considerable stability of EEG state from trial to trial, it was also clear that there was a great deal of fluctuation from state to state in the course of the experiment. The most striking changes in RT occurred in and at precisely those times when there were sudden shifts in the frequency composition of background EEG rhythms.

INSERT TABLE III ABOUT HERE

As may be seen in Table III, when any given type of background activity occurred in sequence there was almost equal likelihood for reaction time to

increase or decrease from trial to trial. Thus, when "alpha" was followed by "alpha," RT was faster on the second trial on 47.2% of occasions and slower in 49.1%. When "slow" was followed by "slow," RT was faster on the second trial in [illegible]% and slower in 40.1%. However, when "alpha" was followed by "slow," RT was faster on the second trial in only 19.[illegible]% and slower in [illegible].6%. "Slow" followed by "alpha" resulted in RT faster on the second trial in 85.2% and slower in 13.8%.

It is therefore increasing the number of samples of EEG background [illegible], especially sequential samples, enhances their predictive value with respect to reaction-time behavior.

In summary, it seems fair to conclude that there is indeed a strong correlation between certain characteristics of background EEG immediately prior to or during signal delivery and the efficiency of motor response to that same signal. Most recently it has been possible to make much more detailed and refined analysis of rhythmical bioelectrical activity than has been discussed so far by application of computer techniques for spectral or correlation analysis. However, it will be more convenient to return to this subject again after outlining some of the more direct applications of computer technology as seen in another aspect of this same general problem.

B. Evoked potentials

It is now commonly recognized that the cerebral electrical response to a particular single stimulus may not be reliably recorded from electrodes placed over the intact skull of the human subject. The amplitude of "spontaneous" background rhythms ranges between 50 and 150 μ volts; that of the so-called

evoked potentials, 5-10 μ volts. To overcome this unfavorable signal-to-noise [illegible] use has been made of the technique of electronic averaging [illegible] electrical potentials [illegible] of the larger background [illegible] electrical activity, the latter being uncorrelated with the occurrence of stimulation. Indeed the technique is now so commonplace and simple that its underlying assumptions are sometimes overlooked and its extraordinary power not always fully comprehended. It is instructive, for example, to realize that the digital computer has made possible [illegible] between light and electron microscopes. [illegible] an entirely new domain has been opened to investigation, [illegible] with any other exploration of uncharted territory, new signposts, new landmarks and standards of measurement will have to be established so that the data [illegible] can be related [illegible]. Most [illegible] a biological point of view. With these general cautionary remarks we proceed.

Figure 7 illustrates the kind of resolution discussed above. The simple

---

INSERT FIG. 7 ABOUT HERE

[illegible] acoustic-photic stimuli did not result in a discernible [illegible] ongoing electrical activity derived from electrodes placed over the [illegible]

and visual cortices in man. However by means of averaging responses to the [illegible] a clear unequivocal and unique wave shape [illegible] the cerebral response to click and [illegible] as [illegible] light.

Multi-channel tape recordings are made and include not only the EEG tracings themselves, but also the signal markers, the response key, and a pre-pulse which is put only on the tape exactly one second prior to delivery of a signal to the subject. Further processing of the data is done by playing the tapes into the LINC computer after it has been suitably programmed. In one of the programs the computer first measures all of the reaction-times and stores this information in several forms for later analysis. RT's are stored in order of their actual occurrence in real time and also in order of latency from the longest to the shortest reaction-time. The contents of this [illegible] it may then be displayed on the face of a cathode-ray oscilloscope in the form of a distribution curve for all the reaction-times (Fig. 8). Each point

INSERT FIG. 8 ABOUT HERE

on the curve represents a single reaction-time, the longest ones at the left, the shortest to the right of the graph. The horizontal bar at the far left of each curve represents the response failures, here treated as infinitely long reaction times. The two curves in Fig. 8 represent the same data displayed with different gain settings, the one on the right being higher. The parameters to be noted on the display are under the manual control of the computer operator.

They may be used to select any desired segment of the RT distribution. Once this selection has been made the program leads on to computation of the average evoked potential for the stimulus trials corresponding to the RT distribution selected. After viewing the resultant wave form the experimenter may choose another segment of the RT distribution and repeat the computational procedure. In this manner the trials selected for averaging are those that have in common a particular behavioral criterion, e.g. those corresponding to trials with short RT [illegible] between X and Y msec, or those trials in which RT is [illegible] distribution [illegible]. For the purposes of the present [illegible] to demonstrate the differences between averaged evoked potentials taken separately from the four quartiles of the RT distribution (Fig. 9).

INSERT FIG. 9 ABOUT HERE

[illegible] the longest [illegible] consisting [illegible] representing, of course, intermediate [illegible]. [illegible] the top most trace of Fig. 9 is the average evoked potential for the longest RT's while the next three traces correspond to successively shorter RT's.

[illegible] longer RT is associated with lowest overall amplitude, longer [illegible] all components except the first one, and with least complexity of wave-shape. Shorter reaction-times were associated with evoked potentials having progressively decreasing latency and more complex wave-shape, particularly the [illegible]

development of a pronounced negative wave between the first and second positive peaks.

For comparison, the average evoked potential was computed for all quartiles together (trace in Fig. 9). As might be expected, this overall average results in a "smearing" of the fine detail and obliteration of the striking differences exhibited in the tracings computed separately for each quartile. Thus the averaging of the data results in a synthetic wave-form, an amalgam of different [illegible] and a considerable net loss of information.

[illegible] derived from [illegible] where the photic evoked potential appears earliest [illegible]. However, flash induced responses are also seen over other [illegible] areas (Fig. 10). In Fig. 10 one may compare flash evoked potentials [illegible] simultaneously from the mid-occipital (upper trace) and the central [illegible] areas [illegible]. [illegible] that the earliest components [illegible]

INSERT FIG. 10 ABOUT HERE

[illegible] Large components are well [illegible] In fact, the [illegible] differences [illegible] are [illegible] apparent when recordings from the left and right [illegible] are [illegible] illustrated in Fig. 11.

INSERT FIG. 11 ABOUT HERE

In another subject (Fig. 12) there were a sufficient number of failures to allow averaging of those trials separately. This trace may be compared with the averages of Q4 and Q3.

INSERT FIG. 12 ABOUT HERE

The high voltage, long duration, late components in the "no response" tracing may or may not be time-locked but almost certainly represent the "theta burst" phenomenon discussed earlier in connection with response failures.

A third subject (Fig. 13) exhibits a similar pattern of evoked potential change although the differences are smaller than those from the first two subjects.

INSERT FIG. 13 ABOUT HERE

It is significant that almost all reaction times were short in this experiment so that the differences in median RT among quartiles is less than it was in the previous examples. Thus, the degree of change in evoked potential configuration is roughly comparable to the amount of difference in RT between quartiles.

The interaction between experimenter and the LINC computer in the course of data analysis makes it possible to check against the possibility that other variables than RT contribute to the results obtained. One of these other variables might simply be time-on-task. It is possible to make use of the other stored list where trials are arranged in actual order of occurrence. Trials are again divided into quarters, this time without regard to RT, but based only on time of occurrence (T quartiles). Average evoked responses are then computed and

displayed according to T quartiles (Fig. 14). The total data used to compute the averages was exactly the same for Figs. 13 and 14; it is only the arrangement

---

INSERT FIG. 14 ABOUT HERE

---

which has changed. While the wave-shapes in Fig. 14 may differ slightly from one average to the next, there is certainly no systematic pattern of change such as was regularly seen with the data arranged according to speed of response.

Establishment of a correlation between behavioral and electrophysiological events is only a first step. It is encouraging to find that evoked potentials differ at different levels of performance. This finding suggests, but does not prove, that the evoked potential may have informational significance. We are well aware that such a suggestion is a long way from definitive knowledge about which electrical components are significant for each of the many contingent physiologic processes which generate the behavior(s).

III. Period Analysis

Following this analysis of the evoked potential and its relationship to reaction-time, another LINC computer program was developed. The new program performed a period analysis (Burch 1964) of a one-second epoch of EEG. Each sample was triggered by the pre-pulse which had been placed on the analog tape exactly one second prior to signal delivery. The analog EEG data was digitized every two milliseconds throughout the one-second epoch. After "normalization," the intervals between zero crossings were measured and the half period counts thus obtained were stored for each desired frequency.

Display was in the form of a histogram (number of half period counts for each frequency) of those frequencies and frequency bands considered most relevant to EEG data. The range from 2 cy/sec. to 31 cy/sec. was considered useful.

By providing simultaneous frequency characterization of the entire EEG band width for the one-second epoch prior to signal delivery, the period analysis program afforded the much more detailed definition of background EEG features which seemed necessary as noted in the discussion of Section I.

As an initial step the reaction-time distribution curve (Fig. 8) was divided into quartiles in the same manner as was done for the evoked potential study. Histograms of the period analysis of each quartile are shown in Figs. 15 and 16.

Fig. 15 demonstrates the pattern for a midline occipital electrode in one subject while Figure 16 shows that for a central vertex electrode in another subject. In both cases the longest RT's (Q4) were associated with increased counts in the theta range (6-8 cy/sec.). However, in the occipital region (Fig. 15) there was an associated marked decrease in the alpha frequency count and virtually no change in the beta category. In the central vertex derivation, longer reaction-times were correlated rather with a decrease in beta frequencies (Fig. 16) without significant alteration in the alpha band. Conversely, short RT's (Q1) were uniquely correlated with low theta counts and high alpha counts in occipital regions (Fig. 15) and with low theta and high beta in the central area (Fig. 16). Although data from two different subjects are used here for illustrative purposes, the differences shown are not attributable to inter-subject variation but are solely related to electrode placement.

This finding indicates that the search for features which uniquely

characterize background states associated with different response latencies will require greater refinement and detail than has been employed previously in our own or other studies and especially must include electrode placement as a dependent variable. On the other hand, if the background characteristics of a particular place do not correlate with a particular response latency with a probability adequate for prediction, the present observation suggests that the special features in each of several places might be summed so that together they afford a higher predictive index.

IV. Evoked Potential Interactions. Contingent Association

The evoked potential is the electrical sign that the brain (or, more strictly, the tissue from which the potential derives) has been perturbed by an externally initiated event. The energy contributed by the external event (in our case, a click or flash of light) acts only upon the sensory receptors. What is recorded from the brain represents energy contributed by the brain and is defined, therefore, as a response to the stimulus. In reality, of course, the compound evoked potential includes elements which, with respect to a given level such as the cortical receiving area, are mainly afferent, elements which reflect intracortical "reaction" processes and, presumably, events assignable to efferent, corticofugal activity. What constitutes "response" for the lateral geniculate, for instance, is "stimulus" for the visual cortex. Many of these elements have been extensively studied in animal preparations where direct recording of individual evoked responses elicited by synchronous shocks has made this possible (Bishop and Clare, 1953; Amassian, 1964; Bremer, 1958). Although no such detailed investigations of averaged evoked potentials are available,

a number of workers (Rayport, 1965; Domino, 1964; Morrell, 1965) have compared averaged wave-forms from the scalp with simultaneously recorded evoked potentials directly from the cortex in man. The similarities are sufficiently striking to provide grounds for hoping that similar analyses will be equally fruitful in the case of the products of a computed average.

Sensory-sensory interactions have been demonstrated for all afferent systems. Recent extensive documentation has come from Buser et al (1963). In this report, sensory-sensory interactions are studied as part of another approach to the question of whether the wave-shape of the evoked potential reflects the manner in which the nervous system processes the "information" contained in the stimulus.

With the averaging techniques, responses to stimuli in any sensory modality may be recorded from many parts of the scalp, even those far removed from the appropriate sensory receiving area. In the frontal cortex, for instance, some particularly interesting interactions have been noted between potentials elicited by click stimuli and those elicited by light.

Figure 17 illustrates averaged tracings obtained from an implanted epidural electrode under each of the conditions listed. The patient required implantation

INSERT FIG. 17 ABOUT HERE

of a sheaf of electrodes for diagnostic and therapeutic purposes. He had an epileptogenic lesion although the epileptic discharge did not happen to involve the area from which this particular electrode derived.

Note especially that the configuration of the response to click was quite different from that to light. When the two stimuli were paired (time relationships adjusted so that the subject perceived them as simultaneous) the averaged compound response reflected both sensory influences. Immediately after pairing, however, the response to single stimuli was altered from that which obtained prior to pairing. Light alone, when presented immediately after pairing (Fig. 17, line 5) elicited an early component having a much greater resemblance to click-induced activity than anything produced by light prior to pairing (Fig. 17, line 2). The effect was transitory and began to disappear during the second hundred stimulations (Fig. 17, line 7).

Another experiment utilizing the same patient and same electrode illustrates

INSERT FIG. 18 ABOUT HERE

the reverse effect in which the click-induced response (post-pair, Fig. 18, line 4) contains late components evident in the light response (pre-pair, Fig. 18, line 2) but not elicited by click at all prior to pairing (Fig. 18, line 1).

In some normal subjects, using scalp derivations and just liminal stimuli, there was little or no early response to flash over auditory cortex (Fig. 19, A).

INSERT FIG. 19 ABOUT HERE

Conversely, the faint click induced no occipital evoked potential (Fig. 19, B). Averages emerging from paired stimulation (Fig. 19, C) were seen in both cerebral zones and had a more complex form than might be expected from simple

linear summation of the two signals. Following the paired trials, the click alone elicited a response in visual cortex similar in form to that produced in the paired interaction (Fig. 19, D). Although again transitory, this effect persisted for 200 trials. On the other hand, the flash alone did not elicit a corresponding response in auditory cortex (Fig. 19, E).

In another normal subject a more extended series of trials (400) was carried out under each stimulus condition (Fig. 20). Following the paired trials (Fig. 20, C), the decay of the click-evoked occipital response (Fig. 20, D) may

INSERT FIG. 20 ABOUT HERE

be seen quite clearly. The successive averages of 100 stimulations each afford some indication of the reliability of these measures, as well as illustrating graphically how transitory changes might be washed out if inappropriately large numbers of trials had been averaged together.

These interactions are extremely sensitive to the presence of both irritative and destructive CNS lesions. Although it is far too early to formulate general rules about effects of various lesions, we have obtained consistent results in three patients having in common irritative, epileptogenic lesions of auditory cortex. The inference that auditory cortex was involved did not rest solely upon the finding of temporal lobe spike discharge but was corroborated by clinical evidence of altered auditory perception during ictal episodes.

Figure 21 shows that prior to paired trials, the light stimulus produced an

INSERT FIG. 21 ABOUT HERE

evoked response in both auditory and visual areas (Fig. 21, A), whereas the click elicited a response only in the auditory cortex (Fig. 21, B). Again following 100 paired trials, the click or light separately were presented. Click produced no alteration in visual cortex while light elicited an augmented response over auditory cortex. The pattern therefore is opposite to that found in the normal subject.

A second patient (Fig. 22) revealed essentially the same changes. In

INSERT FIG. 22 ABOUT HERE

the third patient with ictal alteration of sound perception it was possible to obtain bilateral recording from auditory and visual areas in a case where we knew the lesion was limited to the left hemisphere. In this situation the post-pair flash

INSERT FIG. 23 ABOUT HERE

stimulus (Fig. 23, D) elicited an augmented evoked potential only in the lesioned cortex and not in the normal right side. The interaction on the right, recorded simultaneously, revealed a normal pattern (Fig. 23, C and D).

These findings are consistent with previous observations (Morrell, 1957; Morrell, Naquet and Gastaut, 1957) on experimental epilepsy in animals. Epileptic tissue is more than normally responsive to stimulation via any sensory

modality. Yet once activated the epileptic area seems unable to participate in normal transactional processes as expressed in the capacity to form temporary connections with other functional systems.

Of more general significance is the possibility that evoked potential interactions associated with "contingency" are sensitive to very subtle or minimal perturbations of central integrative function. As all the conditions which produce variation in these interactions become known, this technique should afford an objective assessment of exactly those neural functions so often disrupted in what is now considered a patient group with "minimal brain damage." These individuals, usually children, are those with reading disorders, speech difficulty, perceptual impairment, distractibility, and some forms of so-called mental retardation. Such patients are particularly frustrating to the neurologist and pediatrician because there are usually no signs of gross motor or sensory impairment detectable on neurological examination. Some neurologists may even report that the patient is "neurologically normal" despite behavioral evidence of disabling intellectual impairment not attributable to psychological factors. The situation in the extreme is analogous to having a patient with urinary symptoms examined by a cardiologist who pronounces the cardiovascular system intact. No one would consider such a medical examination as relevant to the patient's problem. Yet it is just as inappropriate to conclude that a negative neurological examination limited to motor, sensory and cerebellar systems rules out "brain damage." There is no reason to expect that the patient whose symptom is inability to learn to read will show an abnormality when his tendons are tapped with a reflex hammer.

The task of the neurologist is to detect, to understand, and to treat disorders

of the nervous system whether gross or subtle. The greatest portion of the brain is in fact not concerned with elementary motor and sensory functions. Appraisal of the functional integrity of brain systems having to do with information processing and transfer is a difficult but essential task for the neurology of the future. Nor can the neurologist be content to leave this matter to the psychologist. Behavioral tests measure only the end result of what may be a complex and multiply-determined process.

We are reasonably confident that the analysis of stimulus-locked potential changes now made possible through application of computer technology will ultimately reveal many intimate details of the manner in which the nervous system processes information. In a preliminary way the data outlined above suggests that these techniques may also provide insight into the mechanisms by which CNS lesions interfere with these processes.

V. Spatial Distribution of Averaged Evoked Potentials

Before it is possible to draw any firm conclusions based upon averaged evoked potentials a good deal more will have to be learned about the neural elements (and, perhaps, non-neural elements) which give rise to them. Although this reservation applies also to work based upon direct recording of single responses, it is especially pertinent, as will be shown, for interpreting the product of a computed average. For example, it is usually assumed that the major portion of the EEG and the directly recorded single evoked response result from the activity of superficial cortical elements in the immediate vicinity of the electrode. However, the higher resolution embodied in the averaging procedure might considerably extend the "receptive field" of the recording electrode allowing discrimination of potential

changes taking place at surprisingly distant sites. Thus volume conducted events, if they are time-locked with the stimulus, might seriously contaminate supposedly local recordings.

For the clinical electroencephalographer the problem of separating volume-conducted from neuronally-propagated potentials represents almost an everyday task. The localization of abnormal discharges requires resolution in depth as well as on the surface. This is one of the major reasons why electroencephalographers have always insisted upon recording simultaneously from as many scalp areas as equipment would allow. Particular montages are chosen not only to sample all of the available scalp surface, but so that whenever an abnormal transient occurs the electrode arrangement maximizes the possibility of measuring the spatial distribution of the abnormal potential. Maps of the instantaneous potential contour for a specific electrical event may be constructed. The distribution of values may be treated mathematically according to well-established principles of volume conductor theory to provide a rough approximation (within limitations imposed by boundary conditions and an inhomogeneous medium) of the depth of origin of the discharge. However, in addition to the limitations noted above, the accuracy of the calculation is compromised by the difficulty of distinguishing the identical event in all areas when it is both immersed in competing background rhythms and distorted by the effects of neuronally propagated activity.

Computer techniques which enhance time-locked events at the expense of unrelated background rhythms seem ideally suited to more accurate solution of this problem. Yet despite the recent flurry of publications on application of computer techniques in neurophysiology we are aware of no report of potential

contour analysis directed at separation of volume-conducted from neuronally-propagated discharge. The remainder of this report is devoted to the results of our own attempts to apply computer techniques to this issue.

Although the main clinical value of potential contour mapping relates to the distribution of abnormal wave-forms, we began our own work with the analysis of evoked potentials. The reason for this choice was that abnormal transients (such as the spike discharges of focal epilepsy or the delta waves of cerebral tumors) occur at unpredictable times and exhibit such variable morphology that programming the computer to "recognize" them with sufficient reliability to permit averaging is a formidable task. On the other hand, since the evoked potential may be triggered by a known stimulus timed by the experimenter, the computer can be programmed simply to digitize the necessary number of intervals beginning with the stimulus marker. The parameters of the stimulus marker are set by the experimenter and remain fixed. Stimuli are recorded on a separate channel of the magnetic tape and therefore are not distorted by ongoing electrical activity of cerebral origin. The problem of pattern recognition is thereby greatly simplified and averaging or other computation is relatively easy. Availability of multichannel magnetic tape recording made it possible to sample a sufficiently large number of areas simultaneously so as to obtain reasonably detailed contour maps for a given plane of derivation. Both light and acoustic (barely audible click) stimuli were used but we shall restrict this discussion to the click-evoked response.

Perhaps the most important new finding was the evidence for maturational changes in potential contour. Figure 24 illustrates the developmental changes

observed in the click-evoked potential contour beginning with the premature

INSERT FIG. 24 ABOUT HERE

infant (birth weight = 1000 gms.). The pattern is even more dramatic when the electrodes are arranged in transverse perspective (Fig. 25). The double-peaked

INSERT FIG. 25 ABOUT HERE

contour of the two-year-old approaches that of the normal adult subject shown in Fig. 26. Note that the analysis time for the adult was 256 msec. as compared

INSERT FIG. 26 ABOUT HERE

with 128 msec. in the infants and children. However, the maps are comparable since only the trough-to-peak amplitude of the first early component was used for construction of that for the adult. It is interesting that in the anterior-posterior electrode arrays (second and third sections of Fig. 26) the potential peak for the adult was somewhat more posterior than the corresponding peak in the infant (third section of Fig. 24) suggesting that with growth there occurs a shift in the relationship of brain to skull landmarks resulting in apparent backward migration of auditory cortex.

The major difference between the adult and the premature or newborn infant in this study was the flat surface potential contour of the latter as contrasted with the pronounced peak of much higher amplitude characteristic of the adult.

We will discuss the significance of this observation later.

First, however, it seems appropriate to indicate [illegible] these potentials are of neurogenic rather than myogenic [illegible] profitable to dwell on negative evidence but it should be mentioned that we have systematically recorded from many muscle groups in a number of subjects and have not seen the short latency (7-8 msec.) averaged evoked potential described by Bickford (1964). We believe the discrepancy to be attributable to the low intensity of acoustic stimulation used in our experiments and perhaps to the smaller sample size (100) which we use for averaging. In our hands the latency of the peak of the earliest component of the auditory evoked potential ranges between 24 and 34 msec.

More positive evidence is afforded by a number of patients in whom there has been an opportunity to record from chronically implanted extradural and intracerebral electrodes. These latter derivations as compared with those from the scalp show higher amplitude, sharper waveforms, but generally the same series of deflections at comparable times are also seen in scalp recordings. Fig. 27 shows a comparison of dural bipolar and monopolar records taken simultaneously

---

INSERT FIG 27 ABOUT HERE

---

with records from the scalp (T_5 in the 10-20 system) and an electromyogram from the right forearm.

The gross similarity between waveforms recorded from intracranial electrodes and those on the scalp argue strongly that all components are neurogenic

that least originate within the cranial cavity. Even if [illegible] potentials might penetrate by volume conduction [illegible] as cortical potentials do to scalp, it seems hardly likely that they would be larger in amplitude intracranially than extracranially.

One of our patients with intractible epilepsy had had shields containing 16 electrodes each implanted symmetrically over both hemispheres so that the most medial point in each array was near the mid-line parasaggitally while the most lateral lay on the temporal lobe (Fig. 28). Fig. 29 illustrates the averaged

INSERT FIG. 28 ABOUT HERE

evoked potentials (N = 100) to light and to click obtained from each electrode position as designated. The total sweep for these records was 512 msec. Sampling

INSERT FIG. 29 ABOUT HERE

rate was 1 msec.

It will be recalled that the potential contour maps shown previously were based upon much simpler records having a smaller analysis time (128 or 256 msec) and only a single major component to be measured. As the analysis time was extended it became obvious that there were several components which were consistently brought out by averaging and, therefore, were presumably time-locked to the stimulus. For example, most of the acoustic evoked potentials illustrated in Fig. 29 contain at least [illegible] distinct oscillations. [illegible] to adequately describe this data would require families of curves. Thus, Fig. [illegible]

shows the voltage distribution for the fourth positive wave. Similar graphs

INSERT FIG. 30 ABOUT HERE

could be made for each peak, and, indeed, would be necessary to characterize the time-locked potential variations for a given plane of recording and for each stimulus. Additional data reduction seemed highly desirable.

Accordingly the LINC computer was programmed to perform a sequence of cross-correlations between the wave-form at one end of the chain of electrodes with each of the other evoked potentials in the array. The entire 512 points were used. The computer found and plotted the correlation maximum of a given wave-form with itself and the others and also the lead or lag of the correlation maximum for the other evoked potentials with respect to the wave-form chosen as reference. Such plots provide not only a comparison of latency differences among peaks but also some estimate of the coherence of wave-shapes over the series.

Fig. 31 demonstrates the series of averaged auditory evoked potentials from each epidural electrode over the left or normal hemisphere in this same

INSERT FIG. 31 ABOUT HERE

patient. On the right of the figure there is a graph of the lead or lag of the correlation maxima. Points above the zero line indicate that the correlation maximum for a particular electrode position lags that for the reference electrode (No. 11, temporal) while points below zero indicate that they lead the correlation maximum of electrode 11 with itself), by the indicated amount of time. In the

[illegible] there are several "legs" to the curve which suggested [illegible] composite of different, independent, and [illegible]

Therefore the computer program was altered [illegible] so that the cross-correlation function could be performed between any chosen segment of the 512 msec. sweep and corresponding segments of all other traces. A particular averaged wave-form is displayed on the oscilloscope (Fig. 32). The

INSERT FIG. 32 ABOUT HERE

experimenter then positions by hand two vertical lines to designate the beginning and end of the segment to be used for the calculation. In this instance two segments were selected: a 90 msec. portion containing the early components, and a 350 msec. portion comprising the late wave. The lead/lag of the correlation maxima of these two segments separately is shown graphically.

With the "window" technique much more linear graphs are obtained. These may be interpreted to mean that for the early components (left, Fig. 32) activity appears first at electrode 12 and successively later at electrodes 13, 14, 15, 16, 17, 18, 19 and 20. However, the late component (right, Fig. 32) arises near the vertex (electrode 20) and propagates laterally and inferiorly so that electrode 11 lags all other positions in sequential and linear fashion. Similar patterns for early and late components have been obtained from electrodes resting on the scalp of a normal human subject (Fig. 33). Fig. 33 illustrates the averaged evoked

INSERT FIG. 33 ABOUT HERE

[illegible] that potential contour graphs and [illegible] of the latter for early and late components.

In marked contrast the same graphs for the premature [illegible] and

INSERT FIG 34 ABOUT HERE

newborn infants (Fig. 35) reveal not only flat surface potential contours but also

INSERT FIG 35 ABOUT HERE

lead lag plots which contain no evidence of propagating wave-fronts. Activity seems to reach all electrode positions at the same instant in time suggesting a common source approximately equidistant from all recording points. In other words, the surface potential contour patterns obtained in premature and newborn children were interpreted as reflecting a largely volume-conducted event arising from a distant, deep and midline source. A biologically appropriate generator would be the medial geniculate nucleus of the thalamus. The location of the medial geniculate body is certainly one which meets the mathematical and physical constraints of the volume conductor model although other thalamic sites would do as well.

It is of considerable interest in this connection that the developmental sequence shown in Figs. 24 and 25 is one which closely parallels the gradual myelinization of human thalamo-cortical radiation fibers (Flechsig, 1876). Thus if the foregoing interpretation is proved correct, the spatial distribution of an averaged evoked potential would provide a sensitive index of the maturation of

thalamo-cortical interconnections.

Contour patterns in the adult, particularly the lead/lag of the cross-correlation, indicate the existence of predominantly propagated events having sources much closer to the lateral surface of the hemisphere. It is inferred that these sources are actually in primary receiving and association zones of the cerebral cortex. The complex early potentials (early window, Figs. 32, 33) are presumed to arise in auditory and para-auditory cortex and thereafter to propagate at a relatively slow rate both ventrally over lateral temporal cortex (lag of electrode 11 with respect to 12, Fig. 32, and of 1 and 6 with respect to 2 and 7, Fig. 33) and dorsally over the frontal cortex toward the vertex. The large late potential (late window, Figs. 32, 33) seems to be quite independent of the short latency complex, arises from a larger area of fronto-parietal cortex near the vertex and propagates ventrally with the same velocity as the early component, to the temporal lobe.

Two qualifications need be kept in mind. We imply in the above statement that the propagation is transcortical because of the almost linear rate and progression exhibited especially by the late component and also because of the similar velocity of propagation of both components. However, the data might theoretically be explained equally well by successive subcortico-cortical relays producing successive "standing" depolarizations. This latter possibility seems less likely to us since we are unaware of any anatomic pathway having exactly the required characteristics. And to postulate two such unknown pathways or one which is accessible in different directions to the two evoked components seems, at the moment, an unreasonable strain on the imagination. In any

event, the appropriate control experiments are currently underway in animal preparations, although it is recognized that these cannot crucially answer the question for the human. Hopefully, a case of human pathology with the necessary limited transcortical lesion will soon present itself for definitive study in our laboratory or in other centers.

Very few previous studies are directly relevant to the understanding of these results. Evidence for transcortical propagation of seizure discharge and the more indirect observations on spontaneous rhythms may be different kinds of phenomena. The only studies employing analogous recording techniques (Lilly and Cherry, 1954, 1955; Livanov, 1960; Walter, W.G., 1953; Remond, A., 1964) for evoked potentials have also been interpreted as showing transcortical spread. Buser and Borenstein (1959) adduced evidence against transcortical spread from primary to "secondary" as is consistent with our findings, but they did not specifically investigate local spread of each response separately.

The second qualification concerns the unitary character of what we have termed the "early complex." It may be that still further segregation of components should be explored. In fact the lesser linearity and the several "legs" prominent in the lead/lag plots for the early window (as compared with the late window) might suggest just such a conclusion. However, our present methods of analysis carry the limitation that the cross-correlation loses accuracy when sample size is reduced significantly below that used in the "early window." For the moment, therefore, we prefer to accept this limitation and consider the present data to be accurate at least to a first approximation.

When the large, rapidly conducting thalamo-cortical radiation fibers

become myelinated and fully functional, evoked activity apparently reaches the cortical level after an extremely brief thalamic delay. Thus the short latency cortical events are almost contemporaneous with those in the thalamus; certainly the series of potential changes overlap at the two sites. In the adult, therefore, even in an averaged response the thalamic component would be swamped by the higher voltage cortical contribution.

If it is correct to interpret the isopotential contour and flat lead/lag plot of the cross-correlation observed in premature and newborn infants as reflecting volume conduction from a midline source, there should be some special circumstances under which this potential might be unmasked even in the adult nervous system. From time to time we have had the opportunity to study some clinical cases, the results of which confirm the foregoing prediction.

Early in our investigations we recorded from a patient with a large destructive glioblastoma involving the entire left temporal lobe (Fig. 36). The analysis time was limited to 128 msec, so only short latency components were

---

INSERT FIG. 36 ABOUT HERE

---

visualized. Fig. 36 demonstrates the averaged acoustic evoked potentials and the surface potential contour maps (anterior-posterior arrays) for the side of the lesion (above, Fig. 36) and for the normal hemisphere (below, Fig. 36). Over the lesioned hemisphere the contour had a flattened configuration and lower overall amplitude highly reminiscent of that seen in the premature and newborn child (Fig. 24). This is the pattern expected when cerebral cortex is absent

or non-functional.

A more recent example is that of an anencephalic infant (Fig. 37). The

---

INSERT FIG. 37 ABOUT HERE

---

contour map was again flat (note the scale: the gain was 5 x that in most other figures) and the lead/lag of the cross-correlation remained close to zero across the head.

Finally, we examined a patient who had undergone a total left hemispherectomy in 1962. Fig. 38 illustrates the post-excision EEG which

---

INSERT FIG. 38 ABOUT HERE

---

revealed no evidence of background electrical activity emanating from the absent hemisphere. Fig. 39 shows averaged (N = 100) acoustic evoked potentials from

---

INSERT FIG. 39 ABOUT HERE

---

each side of the head. As the contour illustrates, there was a peak in amplitude in the right temporal area but no discernible gradient on the left. Nevertheless, there was a definite evoked potential evident in all left-sided derivations.

The cross-correlation analysis (with "window" option) was used for this data. Fig. 40 shows a plot of the correlation maxima for the sequential correlations

---

INSERT FIG. 40 ABOUT HERE

---

beginning with electrode 1. As the midline was reached (electrode 6) and thereafter, the value of the correlation maximum for the early window dropped to zero. For the late window, on the other hand, correlations remained high across the head. This may be interpreted as meaning that the early components on the left are uncorrelated with those on the right and presumably represent a different process. The late components on the left do show a significant correlation with long latency right-sided potentials. Fig. 41 demonstrates the

INSERT FIG. 41 ABOUT HERE

graphs of the lead or lag of the correlation maxima for early and late components (above and below, respectively) on each side of the head. The right hemisphere exhibits the normal adult pattern as we have seen it before. Early components emerge in the temporal region and migrate toward the vertex; late components arise near the vertex and propagate laterally and ventrally. Potentials derived from the left hemisphere show no deviation from zero (early components) and very little for the late events. The early components are non-propagating and arise from a single midline source. The late components are also non-propagating but may deviate slightly from zero because they represent volume conduction of the late, propagating wave on the right. The fact that there was substantial coherence (Fig. 40) between late events in the two hemispheres corroborates this interpretation.

This last case affords a dramatic example of "unmasking" of volume-conducted time-locked potentials after excision of a cerebral hemisphere.

Tracings from the control hemisphere indicate that such activity is normally submerged by the higher amplitude activity of cortical origin.

The sensitive averaging techniques currently employed to detect weak time-locked signals in the presence of higher amplitude background "noise" reveal a composite of volume-conducted and neuronally-propagated activity. By use of multichannel recording devices and proper data analysis aided by computer techniques it is possible to assess the relative contribution of electrical and neuronal processes to the genesis of any particular wave-form. It has been shown that this distinction is potentially useful when applied to some basic, ancient and everyday issues in clinical electroencephalography. Furthermore, there exists a maturational pattern in man such that the relative proportion of volume-conducted as against neuronally-propagated activity serves as a sensitive index of developmental level - information which may not be obtainable in any other way.

The peculiar pattern of transcortical propagation observed for the acoustic evoked potential is a new finding and an especially intriguing one when viewed in the context of biological purpose. What possible functional role could trans-cortical wave propagation play? We are used to thinking of the nervous system in terms of rather precisely defined networks and, in modern days, mainly vertically oriented systems. Some years ago, in a speculative mood, Grey Walter (1953) suggested that the alpha rhythm might behave as a scanning device having properties similar to that of a television receiver. Very recently, Ross Adey (1964) on the basis of his own computer studies has resurrected the notion that travelling waves may play a role in cortical integrative action. And many years

ago, without benefit of any neurophysiological data but after analysis of an incredible volume of behavioral information, Karl Lashley (1942) suggested that interaction of wave trains might very well be the optimal way to explain cortical function and the only way consistent with his behavioral observations.

We have no doubt that we are still a long way from a concrete understanding of these phenomena or a resolution of these questions. But if computer techniques applied to brain physiology generate new models of neural function, the long-range contribution will be far more important than whatever immediate practical implications they may have for solution of current problems.

Acknowledgments

We acknowledge with gratitude the help of Richard Robinson, David Hellerstein, and William Bouris in computer programming.